UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/608,783	06/27/2003	Sanjay Kumar Nigam	1034123-000083	8109

41790 7590 03/05/2007

BUCHANAN, INGERSOLL & ROONEY LLP
P.O. BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
FORD, ALLISON M	
ART UNIT	**PAPER NUMBER**
1651	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/608,783	NIGAM ET AL.	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/7/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-67* is/are pending in the application.

4a) Of the above claim(s) *8-67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-7* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 May 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

Applicant's Request for Continued Examination filed 7 December 2006 has been received and entered into the case. The amendments and arguments submitted, but not entered, after final (received16 October 2006) have been entered. Claim 2 has been cancelled. Claims 1 and 3-67 remain pending, with claims 8-67 being withdrawn from consideration. Claims 1 and 3-7 have been considered on the merits.

Response to Arguments

Applicants' arguments received 16 October 2006 have been fully considered. Objections/rejections not repeated herein have been withdrawn.

Regarding the priority claim of the instant application, applicants argue that because the prior filed applications 09/565,651 and 09/595,195 provide support for claims 1 and 2 (now cancelled) the priority claim is proper. Applicants have corrected the first line of the specification to note the priority claim to these parent applications.

In response, applicants' statement with regards to priority is not understood: it was noted that claims 1 and 2 (now cancelled) are supported by the parent applications, it is claims 3-7 which are not supported by the prior filed applications 09/565,651 and 09/595,195. As such, for purposes of determining patentability, claims 3-7 are considered to have an effective filing date of 28 June 2002, the filing date of provisional application 60/301,684, which provides the earliest support for the claimed subject matter (specifically identification of pleiotrophin as the active component in BSN-CM).

Regarding the rejection of claims 3-7 under 35 USC 112, first paragraph, as lacking written description for the active fragments of pleiotrophin and heregulin, and or functional equivalents of GDNF and FGF1, applicants have submitted documents that show that at the time the invention was made, the active portions of pleiotrophin and heregulin were known, as well as functional equivalents of GDNF and FGF1. Therefore, in view of the cited references, the rejections of record are withdrawn, as the skilled artisan would be able to immediately envisage the claimed invention, in its entirety, based on the knowledge generally available in the art.

Regarding the rejection of claims 1-7 under 35 USC 112, first paragraph, as lacking enablement for use of heregulin, by itself, to propagate UB cells, applicants have amended the claims to eliminate the alternative language that involved use of heregulin in the absence of pleiotrophin. The amendments to claims 1 and 3 renders the rejection of record moot. However, new grounds of rejection have been set forth due to the amendments.

Regarding the rejection of the claims under 35 USC 103(a) over Sakurai et al (PNAS, 1997) in view of Current Protocols in Cell Biology and Naughton et al, applicants provide the same arguments which were addressed in the Final Office Action (mailed 7 July 2006), in order to not burden the record, applicants are directed to the response found in the previous action.

Regarding the rejection of the claims under 35 USC 103(a) over Qiao et al, in view of Current Protocols in Cell Biology and Naughton et al, applicants argue that Qiao et al fails to identify the specific factors which are required for branching morphogenesis in kidney tissue, and in fact teaches away from heparin binding proteins less than 100 kDa. Applicants argue the examiner has otherwise relied on improper hindsight to construct the rejection of record.

These arguments are not found persuasive. First, it is noted that the rejected claims do not specify the specific factors within the culture medium, but rather only require a culture medium that comprises heregulin and/or pleiotrophin. Qiao et al uses the same BSN-culture medium; though they suggest a different weight protein as a *possible* key morphogenic factor, this does not constitute teaching away, because the claims do not specify any isolated fraction, or protein weight. Second, regarding improper hindsight, it is again pointed out that the rejected claims do not require isolated pleiotrophin, but rather only require a culture medium which *comprises* pleiotrophin, and optionally heregulin; the BSN culture medium, used by Qiao et al, inherently comprises both heregulin and pleiotrophin; therefore no hindsight reconstruction was relied upon.

Priority

Applicant's claim for the benefit under 35 U.S.C. 119(e) to provisional application 60/426,152 (filed 14 November 2002) is acknowledged. Applicant's claim for benefit under 35 U.S.C. 119 to international application PCT/US02/20673 (filed 28 June 2002), which further claims priority to US provisional application 60/301,684 (filed 28 June 2001), is acknowledged. All claims are appropriately noted in the first paragraph of the specification.

However, the declaration submitted by applicant further notes claims for priority under 35 U.S.C. 120 to applications 09/595,195 and 09/965,651. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 to 09/595,195 and/or 09/965,651 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior applications. The disclosure of the invention in the parent applications and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35

U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 09/956,651 & 09/595,195, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for claims 3-7 of this application. While applicant has incorporated the teachings of 09/956,651 and 09/595,195 into the current application it is required that the parent applications contain the subject matter claimed in the current application, not vice versa. Neither of the prior-filed applications discloses the propagation of ureteric bud tissue in culture in the presence of pleiotrophin and/or heregulin or active fragments thereof. Therefore, the subject matter of claims 3-7 is not fully supported by the prior filed applications.

Claim Objections

While applicant has corrected the spelling of "ureteric" in the first line of claim 1, they have misspelled it in the 9th line of the claim: UTERIC should be URETERIC. Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 3-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The amendments to independent claims 1 and 3 now require that the culture medium, in which the ureteric bud cells are cultured, to not have been "previously elaborated with cells derived from metanephric mesenchyme and does not contain detectable levels of pleiotrophin" this limitation is not supported by the specification as originally filed, and is thus considered new matter.

In direct contrast, the disclosure as originally filed only supports culture of ureteric bud cells in medium which *has* been previously elaborated with cells derived from the metanephric mesenchyme, which *inherently* contains detectable levels of pleiotrophin (the crux of the instant invention). It is noted applicants point to paragraphs 0047 and 0048 of the PGPubs for support, yet a review of this portion, in particular, directly contrasts the new limitation:

> [0047] The invention demonstrates that UBs undergo branching tubulogenesis in the presence of a conditioned medium elaborated by a cell line derived from the MM also isolated from an E11.5 mouse (BSN cells). This suggests that other soluble factors present in BSN-CM are important for UB morphogenesis. These novel factors that are secreted by the MM are important for the development of the collecting system in artificial systems as well as in vivo.

Applicants are required to cancel the new matter in response to this office action.

Claims 1 and 3-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing ureteric bud cells to undergo branching morphogenesis in culture comprising culturing ureteric bud cells in either BSN-CM and/or pleiotrophin, does not reasonably provide enablement for inducing UB cells to undergo branching morphogenesis in culture "which does not contain detectable levels of pleiotrophin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Applicants have amended claim 1 to define the culture medium, in which the ureteric bud cells are cultured, to *not* have been previously elaborated with cells derived from the metanephric mesenchyme (referencing BSN-culture medium) and which does *not* contain detectable levels of pleiotrophin. Claim 3

is ambiguous, as it both requires the culture medium to comprise pleiotrophin, yet then requires the same negative limitation as claim 1; claim 3 and dependents are being interpreted as requiring the culture medium *does not* have detectable levels of pleiotrophin (which would be inherently present in BSN-culture medium).

Prior to the filing of the instant application, it was known that UB cells cultured in the presence of BSN conditioned media (derived from metanephric mesenchymal cells) would surprisingly undergo branching morphogenesis; addition of glial derived neurotrophic factor (GDNF) would increase the rate and degree of branching morphogenesis (See, e.g. Qiao et al, PNAS 1999). However, it was not clear what specific morphogenic factors, present in the BSN-CM, were responsible for the branching morphogenesis. In the present application applicants have set forth evidence that they have discovered the 18 kDa protein pleiotrophin is at least one of the main morphogenic factors responsible for the branching morphogenesis of the UB cells in 3-D culture (See Spec, particularly Pg. 37). Applicants provide surprising evidence that pleiotrophin, a heparin-binding factor, is capable of inducing impressive branching morphogenesis of isolated UB cells. The entire specification is focused on the ability of pleiotrophin as the morphogenic factor responsible for propagation and morphogenesis of ureteric bud cells. The specification clearly states that "conditioned medium secreted by metanephric mesenchyme-derived cells is required for isolated UB branching morphogenesis" (See Spec, Pg. 33, paragraph 00115); and that "pleiotrophin and GDNF alone are necessary and sufficient for the observed branching morphogenesis of the isolated UB" (See Spec. Pg. 38, paragraph 00131). Thus, applicants entire disclosure contradicts the current claims; therefore, claims 1 and 3-7, under the interpretation that the culture medium does not contain detectable levels of pleiotrophin, are not deemed enabled.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 3-7 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention.

Applicants' amended claim 1 is directed to a method of propagating ureteric bud cells in culture, comprising: (a) contacting the cells in vitro with a medium comprising: (i) fibroblast growth factor-1 (FGF-1); and (ii) glial derived neutrophic factor (GDNF), wherein the medium is not previously elaborated with cells derived from metanephric mesenchyme and does not contain detectable levels of pleiotrophin; and wherein the contacting induces the ureteric bud cells to undergo branching morphogenesis to generate a population of cells comprising tubular branches; (b) isolating cells comprising tubular branches; and (c) contacting the isolated cells with the medium of (a).

Applicants' amended claim 3 is directed to a method for the in vitro culturing and propagating of ureteric bud tissue, comprising isolating ureteric bud tissue from mesenchymal tissue obtained from embryonic kidney rudiments; culturing the isolated ureteric bud tissue in a biocompatible matrix in the presence of a culture medium comprising pleiotrophin, and optionally heregulin, or an active fragment thereof, to produce tubular branches within the biocompatible matrix; wherein the medium is not previously elaborated with cells derived from metanephric mesenchyme and does not contain detectable levels of pleiotrophin; and separating the tubular branches to generate bud fragments; and culturing each of the fragments in the biocompatible matrix with the culture medium.

Evidence that claims 1 and 3-7 fail(s) to correspond in scope with that which applicant(s) regard as the invention can be found in the reply filed 16 October 2006 (the current response). In that paper, applicant has stated "the claimed methods are based, in part, on the discovery that morphogenic factors are secreted by metanephric mesenchyme cells. The Applicants have fractionated media conditioned by such cells and have identified at least some of the factors." (Response Pg. 17); also "Applicants submit that such rationale, articulation, or reasoned basis is unlikely in view of the fact that none of the cited

references teach or describe, individually or in combination, any connection between the presence of pleiotrophin in a medium and the promotion of branching morphogenesis." (Response Pg. 18). These statements indicate that the invention is different from what is defined in the claim(s) because the claims currently exclude use of medium which has been conditioned by cells of the metanephric mesenchyme, or pleiotrophin (the active fragment which is responsible for promoting branching morphogenesis), yet clearly the invention is a method of culturing UB cells in the *presence* of such a medium, containing pleiotrophin.

Claims 3-7 are further rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Amended claim 3 requires the culture medium to both *comprise* pleiotrophin or pleiotrophin and heregulin (line 6), and yet, also requires the culture medium to *not contain* detectable levels of pleiotrophin. The claim is ambiguous. Correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3, 6 and 7 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sakurai et al (PNAS, 1997), in view of "Basic Techniques for Mammalian Cell Tissue Culture" (Current Protocols in Cell Biology, 1998), Naughton et al (US 2003/0007954), and "Overview of Extracellular Matrix" (Current Protocols in Cell Biology, 1998).

Applicants' amended claim 3 is directed to a method for the in vitro culturing and propagating of ureteric bud tissue, comprising isolating ureteric bud tissue from mesenchymal tissue obtained from embryonic kidney rudiments; culturing the isolated ureteric bud tissue in a biocompatible matrix in the presence of a culture medium comprising pleiotrophin, and optionally heregulin, or an active fragment thereof, to produce tubular branches within the biocompatible matrix; wherein the medium is not previously elaborated with cells derived from metanephric mesenchyme and does not contain detectable levels of pleiotrophin; and separating the tubular branches to generate bud fragments; and culturing each of the fragments in the biocompatible matrix with the culture medium. Claim 6 requires the biocompatible matrix to comprise cotton, collagen, polyglycolic acid, cat gut suture, cellulose, gelatin, dextran, polyamide, polyester, polystyrene, polypropylene, polyacrylate, polyvinyl, polycarbonate, polytetrafluorethylene, nitrocellulose compound, or a basement membrane composition. Claim 7 requires the gelatin to be treated to contain proteoglycans, Type I collagen, Type IV collagen, laminin, fibronectin, or combinations thereof.

It is noted that claim 3 both requires the culture medium to comprise pleiotrophin, as well as to not contain pleiotrophin in detectable levels. The following rejection is based on the interpretation of the claim wherein the culture medium *does* comprise pleiotrophin.

Sakurai et al teach a method of propagating ureteric bud cells in culture, comprising isolating ureteric bud tissue from embryonic kidney mesenchyme, suspending ureteric bud (UB) cells in an extracellular matrix gel (a biocompatible matrix), and culturing the UB cells in the presence of BSN-CM, derived from BSN cells of the metanephric mesenchyme, or in serum free media supplemented with several growth factors. For culture with the BSN-CM Sakurai et al used two different ECM gels, one comprising 80% type I collagen and 20% Matrigel, and one consisting of only type I collagen (Claims 6 and 7). For culture with the growth factors the ECM gel consisted of type I collagen. Sakurai et al noted that within 24-48 hours UB cells cultured in the presence of HGF, EGF, TGF-alpha, bFGF, IGF1 and

BSN-CM demonstrated tubulogeneic activity (See Sakurai et al, Pg. 6282, col. 2 & Fig. 5); therefore both the BSN-CM and the noted growth factors are considered conditions that induce the UB to undergo branching morphogenesis to generate a population of UBs comprising tubular branches. BSN-CM inherently comprises pleiotrophin and heregulin, as evidenced by the present application; though Sakurai et al did not specifically identify the presence of pleiotrophin and/or heregulin in the BSN-CM, it was still present in the culture medium (Claims 3, 6 and 7).

While Sakurai et al do not specifically teach subdividing the cultured UB cells/branch tips (to generate what applicant calls bud fragments) and resuspending each subpopulation in culture medium and repeating the culture step, it would have been well within the purview of one of ordinary skill in the art, as part of routine animal cell tissue culture methods, to divide and resuspend subpopulations of the UB cells (Claim 3). One of ordinary skill in animal cell tissue culture recognizes the need to routinely subculture cells by dividing and replating/resuspending the animal cells in order to propagate growth and maintain viability of animal cell and/or tissue culture (See Current Protocols in Cell Biology, 1.1.1). Therefore, in order to maintain a viable cell tissue culture the skilled artisan would have been motivated to continually subculture the growing UB cells and would have expected success in doing so because mammalian cell tissue culture techniques are well known in the art.

Regarding the biocompatible matrix material, Sakurai et al teach use of a Matrigel ECM gel supplemented with type I collagen(See Sakurai et al, Pg. 6281, col. 2), as well as pure collagen ECM gels (See Sakurai et al, Pg. 6282, col. 2); however, it would have been well within the purview of one of ordinary skill in the art at the time the invention was made to use a biocompatible matrix comprising any suitable tissue scaffold material treated with any natural extracellular matrix proteins. Suitable biocompatible matrix materials are well known in the art (See Naughton et al); generally materials for three-dimensional tissue culture should allow cells to attach, or be treated so that cells may attach, and allow cells to grow in more than one layer (See Naughton et al, Pg. 2, paragraph 0031). Naughton et al

teach suitable biocompatible matrix materials include nylon (polyamides), Dacron (polyesters), polystyrenes, polypropylenes, polyacrylates, polyvinyls, polycarbonates, polytetrafluorethylene, polyglycolic acid, nitrocelluloses, cotton, cat gut sutures, celluloses, gelatin, collagen and dextran (See Naughton et al, Pg. 2, paragraphs 0032-0033). Naughton et al further teach the biocompatible materials can be further treated with extracellular matrix proteins to enhance adhesion, including collagen, elastin, glycoproteins (See Naughton et al, page 3, paragraph 0040). Additional ECM proteins known in the art to be useful for enhancing adhesion of cells to substrates include fibril forming collagens (including type I collagen), network forming collagens (including type IV collagen), fibronectin, laminin, and proteoglycans (See "Overview of Extracellular Matrix"). Therefore, at the time the invention was made it would have been obvious to one of ordinary skill in the art to alternatively use any known, suitable biocompatible matrix material, such as those taught by Naughton et al, and to treat the matrix material with any of the known cell adhesion-enhancing proteins, such as those described in "Overview of Extracellular Matrix" (Claims 6 and 7). The functional equivalency of the matrix materials is recognized in the prior art; therefore it would have been *prima facie* obvious to substitute any of the known matrix materials for the Matrigel or collagen materials utilized by Sakurai et al for the same purpose of culturing the UB cells. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 3, 4, 6 and 7 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Qiao et al (PNAS, 1999), i n view of "Basic Techniques for Mammalian Cell Tissue Culture" (Current Protocols in Cell Biology, 1998), Naughton et al (US 2003/0007954), and "Overview of Extracellular Matrix" (Current Protocols in Cell Biology, 1998).

Applicants' amended claim 3 is directed to a method for the in vitro culturing and propagating of ureteric bud tissue, comprising isolating ureteric bud tissue from mesenchymal tissue obtained from

embryonic kidney rudiments; culturing the isolated ureteric bud tissue in a biocompatible matrix in the presence of a culture medium comprising pleiotrophin, and optionally heregulin, or an active fragment thereof, to produce tubular branches within the biocompatible matrix; wherein the medium is not previously elaborated with cells derived from metanephric mesenchyme and does not contain detectable levels of pleiotrophin; and separating the tubular branches to generate bud fragments; and culturing each of the fragments in the biocompatible matrix with the culture medium. Claim 6 requires the biocompatible matrix to comprise cotton, collagen, polyglycolic acid, cat gut suture, cellulose, gelatin, dextran, polyamide, polyester, polystyrene, polypropylene, polyacrylate, polyvinyl, polycarbonate, polytetrafluorethylene, nitrocellulose compound, or a basement membrane composition. Claim 7 requires the gelatin to be treated to contain proteoglycans, Type I collagen, Type IV collagen, laminin, fibronectin, or combinations thereof.

It is noted that claim 3 both requires the culture medium to comprise pleiotrophin, as well as to not contain pleiotrophin in detectable levels. The following rejection is based on the interpretation of the claim wherein the culture medium *does* comprise pleiotrophin.

Qiao et al teach isolating ureteric bud tissue from embryonic kidney rudiments of rats and suspending the isolated UB in an extracellular matrix gel (biocompatible matrix) consisting of type I collagen and Matrigel (See Qiao et al, Pg. 7330, col. 1); the UB cells were cultured in the presence of BSN culture media (BSN-CM) and a growth factor mixture containing EGF, HGF, IGF, FGF2, and GDNF for a sufficient time and under sufficient conditions to undergo branching morphogenesis (See Qiao et al, Pg. 7332, col. 1 & Fig. 2-3). BSN-CM inherently comprises pleiotrophin and heregulin, as evidenced by the present application; though Qiao et al did not specifically identify the presence of pleiotrophin and/or heregulin in the BSN-CM, it was still present in the culture medium (Claims 3, 4, 6 and 7).

While Qiao et al do not specifically teach subdividing the cultured UB cells/branch tips (to generate what applicant calls bud fragments) and resuspending each subpopulation in culture medium and repeating the culture step, it would have been well within the purview of one of ordinary skill in the art, as part of routine animal cell tissue culture methods, to divide and resuspend subpopulations of the UB cells (Claim 3). One of ordinary skill in animal cell tissue culture recognizes the need to routinely subculture cells by dividing and replating/resuspending the animal cells in order to propagate growth and maintain viability of animal cell and/or tissue culture (See Current Protocols in Cell Biology, 1.1.1). Therefore, in order to maintain a viable cell tissue culture the skilled artisan would have been motivated to continually subculture the growing UB cells and would have expected success in doing so because mammalian cell tissue culture techniques are well known in the art.

Regarding the biocompatible matrix material, Qiao et al teach use of a Matrigel ECM gel supplemented with type I collagen (See Qiao et al, Pg. 7330, col. 1); however, it would have been well within the purview of one of ordinary skill in the art at the time the invention was made to use a biocompatible matrix comprising any suitable tissue scaffold material treated with any natural extracellular matrix proteins. Suitable biocompatible matrix materials are well known in the art (See Naughton et al); generally materials for three-dimensional tissue culture should allow cells to attach, or be treated so that cells may attach, and allow cells to grow in more than one layer (See Naughton et al, Pg. 2, paragraph 0031). Naughton et al teach suitable biocompatible matrix materials include nylon (polyamides), Dacron (polyesters), polystyrenes, polypropylenes, polyacrylates, polyvinyls, polycarbonates, polytetrafluorethylene, polyglycolic acid, nitrocelluloses, cotton, cat gut sutures, celluloses, gelatin, collagen and dextran (See Naughton et al, Pg. 2, paragraphs 0032-0033). Naughton et al further teach the biocompatible materials can be further treated with extracellular matrix proteins to enhance adhesion, including collagen, elastin, glycoproteins (See Naughton et al, page 3, paragraph 0040). Additional ECM proteins known in the art to be useful for enhancing adhesion of cells to

substrates include fibril forming collagens (including type I collagen), network forming collagens (including type IV collagen), fibronectin, laminin, and proteoglycans (See "Overview of Extracellular Matrix"). Therefore, at the time the invention was made it would have been obvious to one of ordinary skill in the art to alternatively use any known, suitable biocompatible matrix material, such as those taught by Naughton et al, and to treat the matrix material with any of the known cell adhesion-enhancing proteins, such as those described in "Overview of Extracellular Matrix" (Claims 6 and 7). The functional equivalency of the matrix materials is recognized in the prior art; therefore it would have been *prima facie* obvious to substitute any of the known matrix materials for the Matrigel/collagen material utilized by Qiao et al for the same purpose of culturing the UB cells. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Leon B Lankford, Jr
Primary Examiner
Art Unit 1651